REMARKS

Status of the Claims and Amendments to the Specification and Claims

Claims 1 – 24 and 36 – 37 have been previously cancelled. Claims 26, 27, and 35 are presently cancelled. Claims 25, 28 – 34, and 38 - 41 are currently pending. The claims are presently amended merely to facilitate examination. Both the specification and claims have been amended to replace the term "carboxyl" with "carbonyl." Support for this amendment can be found in the numerous examples throughout the application as filed; in particular, see paragraph [0040] and Schemes 2 - 5 with associated examples (*e.g.* Tables 2 – 5) and discussion in paragraphs [00102] – [00181]. Claim 39 has been amended to be dependent on Claim 30, support for the amendment can be found in paragraphs [0047] and [0054].

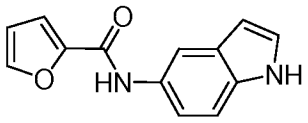
The other amendments to claim 25 are supported in the specification by paragraphs [0019] and [0041]. All cancelled claims and subject matter are cancelled without prejudice to their pursuit in subsequent divisional and/or continuing applications.

Rejection of Claim 25 – 27, 30, and 35 under 35 USC 102(b)

Claims 25 – 27, 30, and 35 stand rejected as allegedly being anticipated by WO 98/06402 ("Johnson"). With respect to cancelled claims 26, 27, and 35, the rejection is moot. Regarding claim 25, and dependent claim 30, the Applicants respectfully traverse.

Claim 25 presently reads, in part (emphasis added), "A composition comprising a *pharmaceutically acceptable carrier, excipient, or diluent* together with a compound of the formula...". For a document to anticipate a claim under 35 USC 102(b), the document must disclose every element of the claim. MPEP 2131.

In the present Office Action, the Office has cited the compound,



(1)

and stated, "Examiner presumes that this compound is in a solvent, which creates a composition." However, the Office did not point to any particular composition disclosed in Johnson which contains (1).

Johnson discloses (1) (see, Example 111 (A)) as an intermediate compound for the preparation of compounds which are not presently claimed. The method of synthesizing (1), in

Johnson, initially prepares (1) in tetrahydrofuran in the presence of triethylamine; extracts (1) with ethyl acetate; purifies (1) via column chromatography with a gradient of dichloromethane containing 0-2% methanol; and recrystallizes (1) from ethyl acetate. Because (1) is merely an intermediate compound in the synthesis of other active compounds, Johnson does not discuss the use of any of the intermediates, which include compound (1), in pharmaceutical compositions.

None of the disclosed solutions of (1) would be considered "pharmaceutically acceptable." We refer to the discussion of "pharmaceutically acceptable carrier, excipient, or diluents" in the specification as filed starting at paragraph [0075] through [0084]. We note the first two lines of [0083], which state,

> *Solutions or suspensions used for parenteral, intradermal, subcutaneous, or topical application can include the following components: a sterile diluent such as water for injection, saline solution, fixed oils, polyethylene glycols, glycerin, propylene glycol or other synthetic solvents...*

However, one skilled in the art would not consider the use of dichloromethane, ethyl acetate, methanol, or tetrahydrofuran as a diluent for the preparation of a pharmaceutically acceptable composition. In fact, such solvents are considered impurities by one skilled in the art, and are to be minimized in preparation of pharmaceutically acceptable formulations.

The Food and Drug Administration has published guidance for the industry for acceptable amounts of residual solvents in pharmaceuticals for the safety of the patient. See, 62 FR 67377. Therein, solvents are classified by potential toxicity, from Class 1 to Class 4. Class 1 solvents "should not be employed in the manufacture if drug substances, excipients, and drug products because of their unacceptable toxicity or their deleterious environmental effect." Class 2 solvents "should be limited in pharmaceutical products because of their inherent toxicity." Class 3 solvents, "it is considered that amounts of these residual solvents of 50 mg per day or less ... would be acceptable without justification." 62 FR 67377, 67380 - 67381. Both dichloromethane and methanol are Class 2 solvents for which "permitted daily exposure" (PDE) should be limited to 6.0 mg/day and 30.0 mg/day respectively. Ethyl acetate and tetrahydrofuran[1] are Class 3 solvents. The foregoing establishes that while limited amounts of these solvents can be tolerated, none are what would be considered a pharmaceutically

---

[1] Remarks regarding solvent classification relate only to the recommendations published in 1997, prior to filing of the instant application and claims. Tetrahydrofuran (THF) was recommended for reclassification by the FDA as a Class 2 solvent in 2002. See 67 FR 6542. THF was reclassified with a recommended PDE of 7.4 mg/day by the FDA in 2003. See *Guidance for Industry, QC3 – Tables and List, November 2003* at http://www.fda.gov/cder/guidance/Q3CT&Lrev1.pdf.

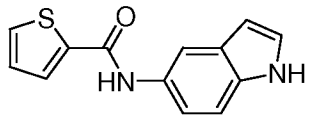
acceptable carrier, excipient, or diluent as defined and used in the present specification and claims.

For the preceding reasons, the Applicants submit that Johnson does not anticipate instant Claims 25, 30, and 35, and respectfully request reconsideration and withdrawal of the rejection by the Office.

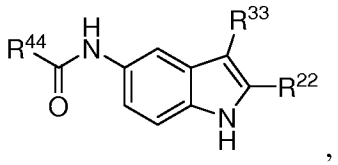
Objection to Claims 25 – 41 for containing Non-Elected Matter

The Applicants acknowledge the objection to the presently pending claims for containing non-elected matter but respectfully traverse in view of the foregoing remarks regarding the rejection under 35 U.S.C. § 102.

In the previous response, filed October 12, 2006, the Applicants elected compositions and methods of using the compound 281,



and suggested the genus of the formula,



,

wherein R^{22}, R^{33}, and R^{44} are as defined in Claim 25.

The Office has alleged that there is at least one Markush alternative that is not novel over the prior art, and subsequently restricted the preceding generic structure to compounds wherein R^{22} and R^{33} are as defined in Claim 25, and R^{44} is optionally substituted C_{3-7} heterocycloalkyl containing at least one N, O, or S atom. Applicants submit that the further restriction of the instant claims, which was based on the allegation that the broader scope was anticipated, is improper in light of the foregoing remarks regarding the outstanding rejection under 35 USC 102(b).

M.P.E.P. § 803.02 sets forth the procedure for restriction and examination of Markush claims:

> *An Examiner should set forth a requirement for election of a single disclosed species in a Markush-type claim. . . . Following election, the Markush-type claim will be examined fully with respect to the elected species, and further to the extent necessary to determine patentability. If the Markush-type claim is*

> *not allowable, the provisional election will be given effect and examination will be limited to the Markush-type claim and claims to the elected species. . . . Should applicant . . . overcome the rejection [e.g., by amendment] . . . the amended Markush-type claim will be reexamined. The examination will be extended to the extent necessary to determine patentability of the Markush-type claim.*

As demonstrated above, the cited art does not anticipate the present claims. Therefore, pursuant to M.P.E.P. § 803.02 the Office must examine the broader scope of the Markush claims. The Applicants have presently amended the claims to facilitate examination of the instant application.

CONCLUSION

Applicants respectfully submit that all requirements of patentability have been met. Allowance of the claims and passage of the case to issue are therefore respectfully solicited.

If the Examiner has any questions or comments regarding this Amendment, they are encouraged to contact the undersigned as indicated below.

Respectfully submitted,

Date: February 6, 2007

By: /Michael S. Greenfield/
Reg. No. 37,142

McDonnell Boehnen Hulbert & Berghoff LLP
300 South Wacker Dr.
Chicago, IL 60606
Telephone: (312) 913-0001
Facsimile: (312) 913-0002